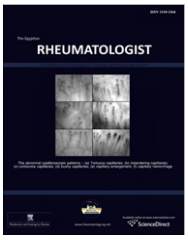
The Egyptian Rheumatologist (2011) 33, 1–11

Egyptian Society for Joint Diseases and Arthritis

The Egyptian Rheumatologist

www.rheumatology.eg.net
www.sciencedirect.com



ORIGINAL ARTICLE

Alveolar hemorrhage in systemic lupus erythematosus: An overview

Geilan A. Mahmoud [a], Rasha E. Gheith [a,*], May M. Kamel [a], Randa A. Soliman [b]

[a] *Rheumatology and Rehabilitation Department, Cairo University, Egypt*
[b] *Critical Care Medicine Department, Cairo University, Egypt*

Received 4 April 2010; accepted 2 June 2010
Available online 31 December 2010

KEYWORDS

Alveolar hemorrhage;
Systemic lupus erythematosus;
Pulmonary vasculitis

Abstract *Introduction:* Alveolar hemorrhage (AH) is a rare, but serious manifestation of SLE. It may occur early or late in disease evolution. Extrapulmonary disease may be minimal and may be masked in patients who are already receiving immunosuppressants for other symptoms of SLE. The capacity of AH to occur and recur despite ongoing immunosuppressive therapy is emphasized.
Aim of the work: Reporting our experience with alveolar hemorrhage in patients with systemic lupus erythematosus.
Patients and methods: Records of SLE patients admitted between years 2000 and 2008 were reviewed. Seven patients with SLE admitted with nine episodes of AH were found. For all study subjects, the pertinent demographic, clinical, laboratory, histologic, therapeutic and outcome data were abstracted and chest X-ray reviewed. The disease activity was assessed using SLEDAI.
Results and Conclusion: The seven patients were females. Their age ranged from 17 to 35 years and disease duration ranged from 4 to 48 months. AH occurred within 4 months of SLE onset in two patients. All patients presented with hemoptysis, new pulmonary infiltrates and hemoglobin drop. Glomerulonephritis was the most common extrapulmonary SLE manifestation (85%). Initial treatment included IV methylprednisolone in all cases (100%), with cyclophosphamide in four episodes. Plasmapheresis (one session) was done in only one episode. Survival rate was 14%.

* Corresponding author.
E-mail addresses: geilanmahmoud@yahoo.com (G.A. Mahmoud), rashagheith@hotmail.com (R.E. Gheith), dr_2mkamel@yahoo.com (M.M. Kamel), randaalysoliman@hotmail.com (R.A. Soliman).

Peer review under responsibility of Egyptian Society for Joint Diseases and Arthritis.
doi:10.1016/j.ejr.2010.02.001

ELSEVIER Production and hosting by Elsevier

Conclusion: Alveolar hemorrhage is a rare but lethal complication of SLE and represents a remarkable challenge. It should be diagnosed promptly with falling red cell indices and new infiltrates on chest radiograph. It occurs in vicinity of active disease. Lupus nephritis is most associated manifestation. Alveolar hemorrhages frequently recur despite ongoing immunosuppressant therapy. Early treatment with intra venous (IV) pulse methylprednisolone and IV cyclophosphamide should be instituted for a better outcome.

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic systemic disease which can often involve many organs systems [1]. The lung is an organ preferentially affected in SLE, and shows various symptoms, including pleuritis, diffuse interstitial lung disease, pulmonary embolism, pulmonary hypertension and pulmonary hemorrhage [2]. The noninfectious pleuropulmonary complications of SLE occur at some point during the disease course in 50–70% of affected individuals. Although these are frequent complications and often responsible for serious morbidity, they account for a very low mortality rate (< 4%) [3].

Alveolar hemorrhage (AH) is a potentially catastrophic and often lethal pulmonary complication of SLE. Among the rheumatologic diseases, AH most frequently occurs in patients with SLE and systemic vasculitis. It is an uncommon complication with reported frequencies ranging from 1% to 5.4% of lupus cohorts [4]. It accounts for 1.5–3.7% of hospital admission due to SLE. However, it is often serious; requiring early, intensive therapy and is associated with high mortality ranging from 23% to 92% [5].

In this article we summarize the course of seven consecutive patients admitted to the Rheumatology and Rehabilitation and Critical Care Departments, Cairo University hospital between years 2000 and 2008. They suffered from nine episodes of SLE-associated alveolar hemorrhage. We compare our experience with reports from the medical literature.

2. Patients and methods

A retrospective chart review was carried out for all admissions of patients diagnosed as SLE from years 2000 to 2008. To be included, patients had to fulfill the revised criteria of the American Rheumatism Association for the diagnosis of SLE [6]. The diagnostic criteria for diffuse alveolar hemorrhage were at least three of the following: pulmonary symptoms, new infiltrates on chest radiographs, a drop of hemoglobin of at least 1.5 g/dl, and a bloody return on bronchoalveolar lavage with hemosiderin-containing macrophage. Severe coagulopathy (INR > 3.5), acute pulmonary edema, or pulmonary embolism was excluded [7].

Onset of AH was defined as the earliest date when pulmonary symptoms (acute or recent development of dyspnea, hemoptysis) correlated with objective clinical findings (chest radiographs demonstrating new pulmonary infiltrates or a drop in hemoglobin level) [5].

Duration of AH was based on the time between onset of AH to the first of two consecutive days when the patient's hematocrit (obtained at least daily) remained stable without need of transfusion [5].

For all study subjects a retrospective chart was done reviewing the following data:

(1) Demographic characteristics.
(2) Clinical data of the patient prior to episode of AH were reviewed including: constitutional manifestations, cardiopulmonary and thrombo-embolic manifestations, cutaneous, musculoskeletal, neuropsychatric, gastrointestinal and urogenital manifestations. Presence of acute or chronic renal failure was reported. Acute renal failure was defined as serum creatinine level exceeding 3.2 mg/dl and chronic renal failure as a 2-fold creatinine rise in [8]. SLE disease activity index (SLEDAI) [9] was reported 3 months prior to attack.
(3) Laboratory investigations done 6 months and 1 month prior to attack of AH were reviewed including: autoimmune profiles in the form of ANA, anti-ds DNA and anticardiolipin antibodies, complete blood counts, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum complement (C3, C4), coagulation profile, liver and kidney functions. Complete urine-analysis and 24 h urinary protein: nephrotic syndrome was defined as daily total urinary protein greater than 3 g and clinical nephritis was defined as proteinuria (> 0.5 g/24 h), microscopic hematuria or cellular cast [7].
(4) Radiographic investigations done including (chest X-ray and CT) prior and during the attack of AH were reviewed.
(5) Histologic studies including renal biopsies performed to the patient classified according to WHO criteria were reviewed.
(6) Treatment of SLE prior to episode of AH and treatment of AH attack were reviewed including dose and duration of: corticosteroids, immunosuppressants, and other treatment modalities.
(7) Presentation of AH in the form of fever, cough, dyspnea, chest pain, hemoptysis, hemoglobin drop, new radiographic infiltrates together with associated extrapulmonary manifestations was reviewed.
(8) Outcome data: survival was defined as the resolution of all symptoms related to AH and discharge in a stable condition [5].

3. Results

Throughout the time period from 2000 to 2008, seven patients with nine episodes of pulmonary hemorrhage met the inclusion criteria in the study. These seven patients represent 1.34% (7 of 522) of patients with SLE admitted to Rheumatology and Critical Care Departments with a diagnosis of SLE.

The range of age of the patients at the time of alveolar hemorrhage was (17–35 years), mean ± SD: 23 ± 6.03. The range of age of the patients at SLE onset was (16–35 years), mean ± SD: 21 ± 6.72. Alveolar hemorrhage occurred within 4 months of SLE diagnosis in two cases and after 24 months in two cases. AH also occurred after 28, 36, 48 months in the other three cases. The range of SLE disease duration was (4–48 months), mean ± SD: 2 ± 16 (Table 1).

The most common SLE manifestations prior to the first attack of alveolar hemorrhage were hematologic and musculoskeletal manifestations. Hematologic manifestations were detected in all of the seven cases (100%) in the form of anemia in all cases and leukopenia in one case (14.2%). Thrombocytopenia could not be detected in any of the cases. Musculoskeletal manifestations in the form of arthralgia and arthritis were also present in all of the seven cases (100%).

The second most common SLE disease manifestations occurring in six out of seven cases (85.7%) were kidney affection and skin manifestations. Mucocutaneous manifestations occurred, in the form of malar rash, photosensitivity, oral ulcers and alopecia.

Serositis in the form of pleuritis and pericarditis with or without effusion was present in five out of seven cases (71.4%). Pleuritis occurred in four cases and pericarditis with effusion occurred in only one case.

Constitutional symptoms also occurred in four out of seven cases (57.2%) in the form of fatigue, fever and weight loss. CNS manifestations were present in three cases (42.2%) in the form of recent cerebrovascular accident, seizure, severe headache not relieved by analgesics and increased intracranial pressure manifested by repeated vomiting and papilledema on fundus examination (Table 2).

Renal involvement in the form of clinical nephritis, nephrotic syndrome, or acute renal failure occurred in six out of seven cases of SLE representing 85.7% being the 2nd most common disease manifestation after the hematologic and musculoskeletal manifestations.

The six cases had undergone renal biopsy and pathological classification according to world health organization (WHO) was done. Four cases had class 4 (diffuse proliferative glomerulonephritis), one case suffered from class 5 (membranous glomerulonephritis) and the last one suffered from class 6 (sclerosing glomerulonephritis).

Six out of seven cases (85.7%) had lupus nephritis. Two out of six cases (33.3%) had nephrotic syndrome and the all six cases were suffering from hypoalbuminemia. The mean urinary protein in 24 h level was 2.65 (ranged from 1.4 to 3.9) g/24 h while the mean serum albumin level was 2.7 (ranged from 2 to 3.2) g/dl in the last 3 months.

Acute renal failure requiring hemodialysis was reported in three out of six cases (50%) (1–2 sessions) and no one required regular dialysis. The mean serum creatinine level in the 3 months previous to the attack was 4.2 (ranged from 1.03 to 7.4) mg/dl. One case (16.6%) had normal serum creatinine and the other five cases (83.3%) had a variable degree of elevated serum creatinine. Hypertension was present in four out of six cases (66.6%) where antihypertensive drugs were received (Table 3).

Alveolar hemorrhage occurred in six out of seven cases (85.7%) already receiving treatment for manifestations of SLE. Five out of seven cases (71.4%) were receiving oral corticosteroids (prednisolone, dose range, 10–40 mg/day), four out of seven cases (57.1%) were receiving monthly IV pulse methylprednisolone ranging 500–1000 mg for three consecutive days and three out of seven cases (42.8%) received cyclophosphamide pulse (ranging 750–1000 mg/m^2) for lupus nephritis. The 4th case received (800 mg/m^2) cyclophosphamide in the last month only. Azathioprine (100 mg daily) was used in four out of seven cases (57.2%) (nos. 2, 3, 4 and 5) and hydroxychloroquine (400 mg/day) was also used in four cases (57.2%). Other treatment was given to all cases which include (antihypertensive and antibiotics).

Immunosuppressive therapy within 1 week before AH had been reported in five out of seven cases (71.4%). One course of IV pulse methylprednisolone (1 g for 1–3 consecutive days) was administered within 1 week prior to pulmonary hemorrhage. Three cases received the pulse due to active lupus nephritis and the other two cases were due to CNS affection. Only two cases were receiving one course of parenteral pulse cyclophosphamide therapy (500–800 mg/m^2) within 1 week prior to pulmonary hemorrhage (Table 4).

Regarding the symptoms and signs of pulmonary hemorrhage, hemoptysis and hemoglobin drop were observed in all episodes (100%). Hemoptysis was initially present as blood

Table 1 Patients' demographics in SLE-associated AH.

Case no.	Sex	Age at AH (years)	Disease duration (months)	Age at SLE onset (years)
Case 1	Female	17	4	17
Case 2	Female	35	4	35
Case 3	Female	23	24	21
Case 4	Female	20	48	16
Case 5	Female	26	28	24
Case 6	Female	19	24	17
Case 7	Female	21	36	18

Table 2 SLE manifestations prior to AH.

Case no.	Heamatologic	Arthritis	Kidney	Skin	Serositis	Constitutional	CNS
Case 1	+	+	+	–	+	–	+
Case 2	+	+	+	+	+	+	–
Case 3	+	+	+	+	+	+	–
Case 4	+	+	+	+	+	+	+
Case 5	+	+	+	+	–	–	–
Case 6	+	+	+	+	–	–	+
Case 7	+	+	–	+	+	+	–
	100%	100%	85.7%	85.7%	71.4%	57.2%	42.8%

Table 3 Renal affection in SLE.

Case no.	Biopsy	Ptn/24 h (g)	Albumin (g/dl)	Creatinine (mg/dl)	HTN	ARF	Nephrotic
Case 1	Class 4	3.9	2.2	2.4	–	–	+
Case 2	Class 5	3	2	3.1	+	–	–
Case 3	Class 4	2	3.1	1.03	–	–	–
Case 4	Class 6	1.4	2.8	6.6	+	+	–
Case 5	Class 4	3.6	3.1	4.5	+	+	+
Case 6	Class 4	2	3.2	7.4	+	+	–

Abbreviations: HTN = hypertension; ARF = acute renal failure.

Table 4 SLE therapy prior to AH.

Case no.	Pred. (mg/day)	Pulse steroid	Pulse CYC	AZT (mg/day)	HXQ (mg/day)	Others
Case 1	–	–	–	–	–	+
Case 2	10	–	–	100	–	+
Case 3	10–25	+	–	100	400	+
Case 4	15–40	+	+	100	400	+
Case 5	20–40	+	+	100	–	+
Case 6	30–40	+	+	–	400	+
Case 7	–	–	–	–	400	+

Abbreviations: Pred. = prednisolone; HXQ = hydroxychloroquine.

tinged sputum and rapidly turns into frank hemoptysis in eight episodes and only one episode (1st episode of case no. 1) showed frank hemoptysis at the beginning of the attack.

Dyspnea and cough were observed in eight episodes (88.8%). The onset of dyspnea was mild in one episode (case no. 4) which rapidly became severe while the other episodes suffered from abrupt onset of severe dyspnea, tachypnea and respiratory distress which required assisted ventilation. Temperature elevation more than 38 °C was noted in six episodes (66.6%).

Chest radiograph was performed in all episodes and it revealed newly encountered alveolar infiltrates in all episodes (100%) of AH. The most common radiographic pattern was bilateral diffuse infiltrates in eight out of nine episodes (88.8%). Unilateral densities which could be easily mistaken for lobar pneumonia were seen in one episode (case no. 4). Bilateral pleural effusion was detected in only one case. HRCT chest performed in four out of nine episodes (44.4%) revealed diffuse alveolar infiltrates which confirms the diagnosis (Table 5) (see Figs. 1 and 2).

Extrapulmonary manifestations of disease during attack of AH are summarized in Table 6. In addition to AH, other systemic involvement had been reported including renal, CNS, hematologic and joint affections. Active lupus nephritis was the most common extrapulmonary manifestations occurring in conjunction with AH attack being present in eight out of nine episodes (88.8%). Neuropsychiatric manifestations including seizure and psychological disturbance in the form of (psychosis, hallucinations, change in mode, depression) occurred within 1 week of AH attack in five out of nine episodes (55.5%). Convulsions were the most common among the CNS manifestations as it occurred in three episodes. The fits preceded AH attack by 1–2 days in cases and followed the onset of the attack in one case. Psychological disturbance preceded AH episodes 3–5 days in two cases. Hematologic manifestations in the form of leukopenia ($<4\times10^3$) were present in two out of nine episodes (22.2%) at the time of AH. Neither thrombocytopenia nor autoimmune hemolytic anemia could be detected in any case at that time. Arthritis was present in one out of nine episodes (11.1%).

Table 5 Clinical manifestations of nine episodes of DAH.

	Episode no.	Hemoptysis	Dyspnea	Cough	Fever > 38 °C	Hb↓	X-ray infiltrate	CT infiltrate
Case 1	1	+	+	+	+	+	+	/
	2	+	+	+	+	+	+	+
Case 2	1	+	+	+	–	+	+	+
Case 3	1	+	+	+	+	+	+	/
Case 4	1	+	+	+	+	+	+	/
Case 5	1	+	+	+	–	+	+	+
Case 6	1	+	–	+	–	+	+	/
	2	+	+	+	+	+	+	/
Case 7	1	+	+	–	+	+	+	+

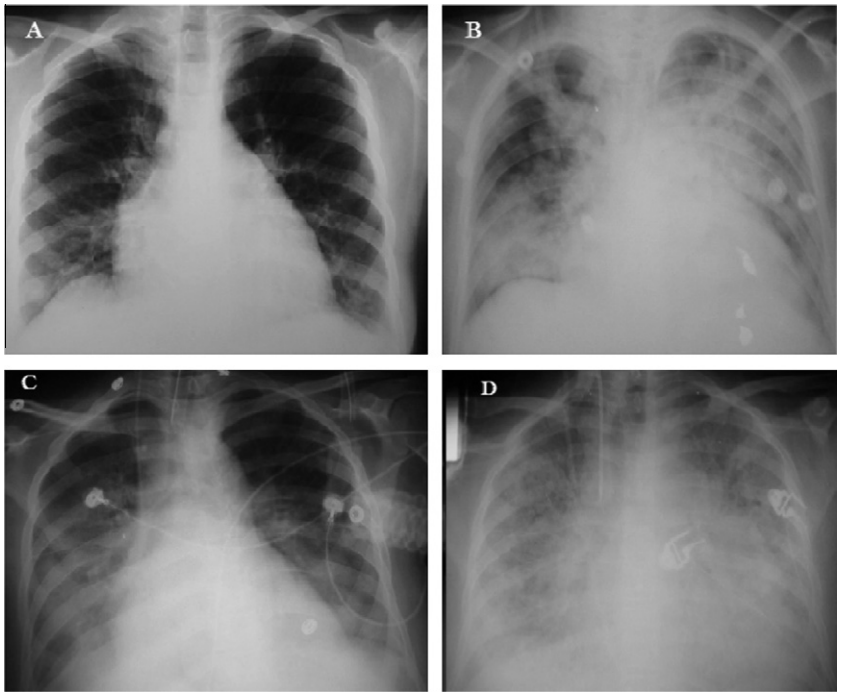


Figure 1 Chest X-rays of second episode of case no. 1. (A) Mild bilateral infiltrates at the onset 1st day of attack. (B) Bilateral ill defined diffuse opacities mostly involving the right lower and left upper zones at the 1st day of attach during frank hemoptysis. (C) Partial resolution of the infiltrates following 5th dose of pulse steroid therapy and pulse cyclophosphamide at 6th day of attack. (D) Bilateral ill defined diffuse opacities mostly involving the whole lungs at 10th day of attack before death of the patient.

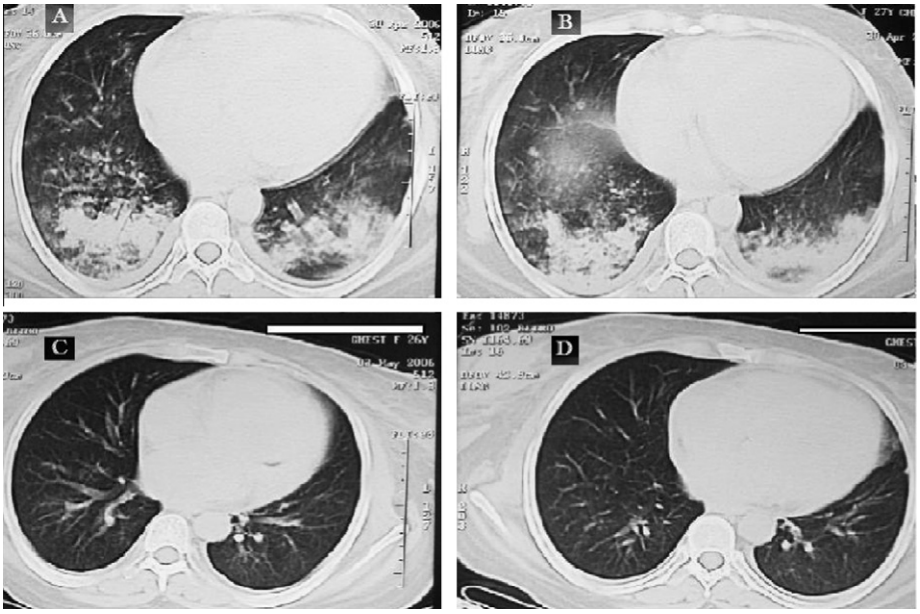


Figure 2 HRCT chest of case no. 5. (A and B) Area of hyperdensity on both lung fields (suggestive of hemorrhage) at the 1st day of attack. (C and D) Complete resolution of both lungs on the 4th day of attack following 3 days dose of pulse steroid therapy (1 g/day).

Disease activity in SLE-associated AH is summarized in Table 7. The spectrum of SLE patients' characteristics varied greatly. The SLE disease activity index was diverse (SLEDAI range: 17–36). Severe disease activity according to SLEDAI (grading: 21–45) was reported in six out of seven cases (85.7%) while moderate disease activity according to SLEDAI (grading: 11–20) was reported in only one out of seven cases (14.3%).

Laboratory findings at the time of diffuse alveolar hemorrhage (DAH) are summarized in Table 8. A drop in hemoglobin

Table 6 Extrapulmonary manifestations of SLE during attacks of AH.

Case no.	Episode	Kidney	CNS	Hematologic			Arthritis
				Leukopenia	Thrombocytopenia	AIHA	
Case 1	1	+	–	–	–	–	–
	2	+	–	–	–	–	–
Case 2	1	+	+	–	–	–	+
Case 3	1	+	+	+	–	–	–
Case 4	1	+	–	–	–	–	–
Case 5	1	+	+	+	–	–	–
Case 6	1	+	–	–	–	–	–
	2	+	+	–	–	–	–
Case 7	1	–	+	–	–	–	–

Abbreviations: AIHA = autoimmune hemolytic anemia.

Table 7 SLEDAI of seven SLE cases suffered from AH.

Case no.	SLEDAI
Case 1	27
Case 2	26
Case 3	24
Case 4	25
Case 5	17
Case 6	36
Case 7	25

level was detected within 48 h from onset of PH in all cases (100%). Hemoglobin drop ranged from 1.5 to 3.2 g/dl (mean 2.3). Platelet count range was 180,000–300,000 cells/mm^3 (mean 249,770). INR range was 1–1.6 (mean 1.17). No coagulopathy or critical thrombocytopenia ($<50{,}000$ cells/mm^3) could be detected in any case and anticoagulation therapy was not reported. Anticardiolipin antibody was negative in all cases (100%). Creatinine level range in seven out of nine episodes was 3.7–5.7 mg/dl (mean 4.9). Anti-double stranded DNA positivity was found in all episodes (100%) and hypocomplementemia was reported in eight out of nine episodes (85.7%).

Treatment of DAH is summarized in Table 9. All episodes (100%) were treated initially with intravenous methylprednisolone, the doses ranging from 500 to 1000 mg/day for 2–5 days. Cyclophosphamide was employed in four episodes (44.4%), it was initially given intravenously as a single dose (range, 500–800 mg/m^2) after steroid pulse. Plasmapheresis was employed in one case (14.3%) as one session on the 4th day of attack and no more sessions as the patient died the next day. Broad spectrum antibiotics was started empirically while cultures were pending in all episodes (100%) and proper isolation of the patients was done to avoid infection. Dialysis due to acute renal failure was done in five episodes (55.5%). Peritoneal dialysis in one case and hemodialysis in four episodes and only one episode required regular dialysis after the attack. All cases required intensive care where assisted ventilation was employed in the form of mechanical ventilation in seven episodes (77.7%) and oxygen mask in two episodes (22.2%).

Outcome of DAH is summarized in Table 10. Recurrence of AH occurred despite aggressive therapy. Recurrent episodes were noted in two cases during follow up period of 1 month. The interval between the two episodes was 21 days in both cases. One case died during 2nd attack as she developed hypoxia, hypercapnia and respiratory arrest while the other case survived the 2nd attack and was discharged from ICU.

Death during admission in ICU has been reported in six out of nine episodes (66.6%). The cause of death was due to respiratory failure. The overall mortality rate was 66.6% (6/9 episodes). On a per-patient basis the mortality was 85.7% (6/7 cases).

Table 8 Laboratory findings in seven cases during attacks of AH.

Case no.	Epi. no.	Hb↓ in 48 h (g/dl)	Platelet (cells/mm^3)	INR	aCL	Low C3 and C4	Anti-ds DNA	Creatinine (mg/dl)
Case 1	1	3	267×10^3	1.2	–	+	+	/
	2	3.2	300×10^3	1.3	–	+	+	3.7
Case 2	1	1.8	184×10^3	1.4	–	+	+	4.2
Case 3	1	1.8	296×10^3	1.1	–	+	+	5.1
Case 4	1	1.5	250×10^3	1	–	+	+	5.7
Case 5	1	2.5	256×10^3	1	–	+	+	4.8
Case 6	1	1.5	285×10^3	1.6	–	+	+	5.3
	2	3.2	230×10^3	1	–	+	+	5.7
Case 7	1	2	180×10^3	1	–	–	+	/

Abbreviations: Hb↓ = hemoglobin drop; INR = international normalized ratio; aCL = anti-cardiolipin antibodies; C = complement; anti-ds DNA = antibodies to double stranded DNA.

Table 9 Treatment of DAH.

Case no.	Episode	Cs	CYC	PP	AB	D	V
Case 1	1	+	+	–	+	HD	MV
	2	+	+	–	+	HD	MV
Case 2	1	+	+	–	+	–	MV
Case 3	1	+	–	+	+	–	MV
Case 4	1	+	–	–	+	PD	MV
Case 5	1	+	–	–	+	–	MV
Case 6	1	+	+	–	+	HD	O_2
	2	+	–	–	+	HD	O_2
Case 7	1	+	–	–	+	–	MV

Abbreviations: Cs = corticosteroids; CYC = cyclophosphamide; PP = plasmapheresis; AB = antibiotics; D = dialysis; HD = hemodialysis; PD = peritoneal dialysis; V = ventilation; MV = mechanical ventilation.

Table 10 Outcome of DAH.

Case no.	Episode no.	Outcome
Case 1	1	Alive
	2	Died
Case 2	1	Died
Case 3	1	Died
Case 4	1	Died
Case 5	1	Died
Case 6	1	Alive
	2	Alive
Case 7	1	Died

4. Discussion

SLE is an autoimmune disease characterized by disturbances in innate and adaptive immune mechanisms. Multiple systems and organs may be involved. Pulmonary disease is a common manifestation of SLE and is reported to occur in over half of the patients throughout the course of their disease [10].

Pulmonary disease in SLE can be extremely diverse, encompassing abnormalities such as pleuritis with pleural effusions, acute lupus pneumonitis, diffuse interstitial lung disease, pulmonary hypertension, pulmonary embolism, diaphragmatic abnormalities, atelectasis and pulmonary alveolar hemorrhage [11–13]. The latter is the most devastating pulmonary complication which was first described by Osler in 1904 [4].

This retrospective study was designed to evaluate the SLE patients with AH in Rheumatology and Rehabilitation, Critical Care Departments, Cairo University.

DAH is a rare fatal complication with reported frequency ranging from 1% to 5.4% of Lupus cohorts [14,15]. It accounts for 1.5–3.7% of hospital admissions due to SLE [16,17]. A lower incidence of DAH (0.52%) was reported by Chang et al. [7]. In the current study, DAH accounted for 1.3% of SLE cohorts. However, in autopsy series, alveolar hemorrhage, appearing as either focal collection of red blood cells or more diffuse involvement, has been reported to occur in as many as 66% of cases of SLE [18].

All patients in the current study were females. However, female prevalence in literature review was 79%. Similar to most reports, most of our patients were young (mean age was 23 years). The mean age in the majority of published reports ranged between 23 and 37.8 years [5,15–17,19].

AH occurred early in the course of disease. The mean disease duration was 2 years. In most patients with pulmonary hemorrhage (PH), the diagnosis of SLE has already been established; however, PH as initial manifestation of SLE is also seen. In most studies, the mean duration of SLE ranged from 1.8 to 4.5 years [5,14–17]. Only one previous study [20] reported PH occurring after a mean duration of 14.1 years of SLE. Although cases of AH as a presenting symptom were reported in some series [5,21,22], we did not report any cases with AH at disease onset.

The onset of AH is abrupt and the symptoms are acute usually developing over hours to several days. This is the case in our study and other series [15–17,23].

Presentation of AH with the "classical triad" of hemoptysis, abrupt fall in hemoglobin level, and new pulmonary infiltrates were present in all cases of the present work. However, this triad was not uniformly seen in other series [16,17,24,25].

In published literature, presentation with hemoptysis is reported with a frequency of 25–100%, compared to 100% in ours [16,25]. Zamora et al. [17] reported hemoptysis in only 42% of the episodes at the time of admission but appeared at some point during the hospital stay in all episodes.

New pulmonary infiltrates (published frequency 83–100%, compared to 100% in our study) accompanied by worsening or new anemia (published frequency 75–100%, 100% in our study) appear to be more sensitive clinical signs.

The absence of hemoptysis is not unique for AH in SLE, having been reported for other etiologies of DAH [26]. In this situation, diffuse pulmonary infiltrates, a falling hematocrit and a sequential hemorrhagic bronchoalveolar lavage point to diagnosis. Although most SLE patients are too ill to undergo this evaluation, a single breath diffusing capacity for carbon monoxide will be elevated, reflecting the increased availability of hemoglobin within the distal airspaces [27]. However, DLco assessment was not reported in our series. This was attributed to the patients' poor and unstable condition.

Acute dyspnea, cough, rales, chest pain, dyspnea and fever >38 °C are frequently present, leading to diagnostic confusion with bacterial and opportunistic pulmonary infections.

Dyspnea was reported in 89% of our studied cases. However, Liu et al. [15] and Santos Ocampo et al. [5] reported

dyspnea in all cases. Again, fever > 38 °C was present in 67% of our studied episodes which was similar to those reported by many authors [5,14,15].

The recurrent nature of AH was of concern, and this frequently occurred without warning. The occurrence of AH despite ongoing treatment with significant dose of immunosuppressive drugs must be noted [5]. This is the case in our study as recurrence of AH was observed in two patients out of the seven studied patients (29%).

Radiographic findings ranging from diffuse alveolar infiltrates to lobar infiltrates and are not specific. Similarly, CT scans and magnetic resonance imaging have been used in PH but its usefulness, especially in ill patient is limited [28,29].

Several radiographic patterns were seen, probably reflecting the location, extent and duration of AH. Although classically described as a diffuse bilateral alveolar interstitial filling pattern, unilateral lobar infiltrates have been reported. None of these radiographic patterns are specific for AH [24,30]. Radiographic studies in the present work revealed newly encountered alveolar infiltrates in all episodes of AH (100%). The most common radiographic pattern was bilateral diffuse infiltrates in eight out of nine episodes (89%). Unilateral densities were seen in one episode. HRCT was performed in four episodes and revealed diffuse alveolar infiltrates.

PH occurred in acutely ill patients with high disease activity estimated by SLEDAI. It was severe in six patients and moderate in one case of the present study. This agrees with Badsha et al. [31] as the median SLEDAI and mean SLAM scores were high and the authors recommended that SLEDAI and SLAM scores should raise the index of suspicion of PH. However, Chang et al. [7] results showed SLE activity at presentation was diverse (SLEDAI range 15–41). They recommended that the physician should be aware of DAH in SLE patients regardless of the disease activity or chronicity. Also, they concluded that APACHE II (Acute physiology, Age and Chronic Health Evaluation) and organ system failure (OSF) scores, but not the SLEDAI, could probably predict the outcome of DAH in SLE.

Many published series emphasize the simultaneous presence of DAH with multiple extrapulmonary manifestations of SLE [15–17,19]. Lupus nephritis was the most common concurrent systemic finding in our patients (6/7) (86%). This was concordant with many previous reports [15–17,33]. It has been reported that active nephritis associated with nephrotic syndrome is the major risk factor for PH in SLE [15]. Nearly, all our patients had proteinuria and two had nephrotic syndrome. Kidney biopsy in our patients revealed diffuse proliferative GN in four cases, membranous GN in one case and end stage renal disease (ESRD) in one case. Serum creatinine was raised in five out of six patients with renal affection. It was measured at time of episodes and the range was (3.7–5.7) mg/dl while before episodes the range was (1.03–7.4) mg/dl. Three patients with five episodes needed dialysis and only one required regular dialysis. Two episodes (2/5) that underwent dialysis survived the attack and the other three episodes (3/5) did not survive. On the other hand, Lee et al. [34] reported 7 SLE patients with DAH. They assumed that azotemia (sCr > 3.0) mg/dl and hemodialysis therapy had no significant association with the increased risk of mortality in their series. Chang et al. [7] reported that the higher serum creatinine or the need of HD did not adversely affect the survival of his patients also.

The second most frequent associated extrapulmonary manifestation was CNS lupus (55.5%). This agrees with Liu et al. [15] who reported 61% incidence of CNS among his patients. However, Santos Ocampo et al. [5] reported only 10% incidence of CNS disease. We reported major CNS lupus preceding three episodes of AH which may highlight the possible role of neurogenic pulmonary edema secondary to CNS lupus as a possible risk factor in the development of DAH as reported by Chang et al. [7].

Arthralgia and arthritis were the least extrapulmonary manifestation associated the AH attacks (11%) in our study. This may be explained by assumption of Santos Ocampo et al. [5] who reported that milder SLE manifestations may have been masked at the time of AH because of ongoing immunosuppressive therapy (see Table 11).

It is generally believed that treatment of life threatening hemorrhage needs to be started promptly because death from respiratory failure can occur within hours to days of initial presentation [35].

Initial treatment included IV methylprednisolone for 3 days and IV cyclophosphamide in four episodes while it was given 1 week prior to the attack in two episodes. All patients required ICU admission. All episodes except two needed to be supported by mechanical ventilation. The other two episodes needed only O_2 mask.

The aggressive treatment did not appear to affect outcome in our group of patients. Corticosteroids were the mainstay of therapy for AH. However, in SLE patients with PH there were no clear indications about which treatment modality influence the outcome. Several authors have recommended the use of high-dose corticosteroids and cytotoxic agents as well as plasmapheresis as soon as the diagnosis of hemorrhage is established [23,35–37]. Most series report a very complicated downhill course in patients with hemorrhage despite aggressive cytotoxic therapy [16,30,35,38]. No correlation between treatment regimens and response rates has been documented and death has often been attributed to respiratory failure [30,33,39,40].

Liu et al. [15] reported that there was no single case of PH without antecedent aggressive corticosteroid treatment and suggested the possibility that high dose corticosteroid therapy itself poses an increase risk of PH in SLE patients. The authors attributed this to connective tissue atrophy resulting from prolonged usage of steroid.

Badsha et al. [31] suggests that increased use of cyclophosphamide may confer a survival benefit. However, Zamora et al. [17] used cyclophosphamide in the majority of their patients and the mortality rate was increased for these receiving cyclophosphamide and they argue that if it is used in an acute episode it contributed to mortality. Based on Cooper et al. [41] assumption that cyclophosphamide could cause hemorrhagic pneumonitis Wu et al. [42] suggested that cyclophosphamide should be used carefully in SLE patients with PH.

In the present study, we reported a poor prognosis with 14% survival. However, there have been some controversies regarding survival rates following attaches of AH in SLE. The highest survival rates have been reported by Schwab et al. [19] and Santos Ocampo et al. [5] with 75% and 100% survival rates, respectively. The lowest survival rate was reported by Abud Mendoza et al. [16] with 8%. Also Liu et al. [15] 23% and Barile et al. [20] 38% showed low survival rates.

Table 11 Characteristics and clinical presentation of patients with SLE-associated AH (current and selected case series from 1985 to present).

Variables	Current	Badsha et al. [31]	Santos Ocampo et al. [5]	Liu et al. [15]	Barile et al. [20]	Koh et al. [14]	Zamora et al. [17]	Schwab et al. [19]	Myers and Katzenstein [13]	Abud Mendoza et al. [16]
Patient characteristics										
Patients, no.	7	22	7	13	34	10	15	8	4	12
% of SLE cohort	1.3	1.4	1	4	5.4	1.4	3.7	1.4	–	1.6
Male/female, no.	0/7	2/22	1/6	1/12	2/32	2/8	5/10	2/6	3/1	0/12
Mean age, years	23	31.6	31.1	26	34.5	26.5	30.1	37.8	29	23
Range, years	17–35	–	19–44	10–50	–	13–44	19–44	17–54	13–51	16–40
Mean duration of SLE, years	2	0.96	4.5	1.9	14.1	1.8	2.5	2.3	–	2
Range, years	4 months–4 years	–	2 weeks–19 years	4 weeks–5 years	–	0–5	0–8	0.1–7	–	0.1–5
(+) Anti-ds DNA, %	100	–	43	61	88	50	–	87.5	75	25
Presenting signs and symptoms of AH, % of episodes										
Hemoptysis	100	50	50	84	58	30	42	100	75	25
New infiltrates	100	100	100	100	100	100	100	87	100	83
Alveolo-interstitial	–	–	80	–	–	100	100	–	100	83
Lobar	–	–	20	–	–	0	0	12	0	–
Bilateral	89	–	80	100	–	–	100	–	100	–
Unilateral	11	–	20	–	–	–	0	12	0	–
Pleural effusions	22	–	30	–	–	–	37	–	–	–
Anemia	100	100	90	100	91	100	94	75	–	100
Dyspnea	89	–	100	100	100	–	–	73	87	
Fever	67	–	80	54	–	90	26	100	25	25
Chest pain	–	–	30	–	–	20	–	–	–	–
Extrapulmonary signs and symptoms accompanying AH, % of episodes										
Renal-nephritis	86	77	70	100	32	40	93	62	–	41
Hematologic										
Leukopenia	22	32	30	23	–	20	0	–	–	50
Thrombocytopenia	0	40	20	61	–	–	31	–	–	–
AIHA	0	–	–	–	–	–	–	–	–	–
Skin-mucositis	0	68	0	38	47	70	73	62	–	41
Arthralgia–arthritis	11	68	10	15	44	30	15	62	–	16
Neuro-psychiatric lupus	55.5	32	10	61	14	20	47	37	–	58
Low complements	86	91	83	84	–	70	–	100	75	25

Table 12 Therapies used, survival, and outcomes of SLE-associated AH (current and selected case series from 1985 to present).

Variables	Current	Badsha et al. [31]	Santos Ocampo et al. [5]	Liu et al. [15]	Barile et al. [20]	Koh et al. [14]	Zamora et al. [17]	Schwab et al. [19]	Myers and Katzenstein [13]	Abud Mendoza et al. [16]
Acute treatment, % of episodes										
Cs	100	100	100	100	100	100	78	100	100	83
CYC	44	86	70	15	5	80	68	62	25	8
AZT	–	–	0	–	0	0	26	0	0	16
PP	14	50	40	–	5	40	36	12	25	–
MV	78	64	30	77	59	80	68	50	75	–
AB	100	–	90	–	94	100	–	75	–	–
Survival, %	14	64	100	23	38	60	46	75	50	8
Follow-up										
Range (months)	–	–	1–22	–	0.1–8	3–108	1–108	0.5–48	–	–

In contrast to poor prognosis shown in most reports, including ours, Schwab et al. [19] had shown optimistic results in their SLE patients with pulmonary hemorrhage. The explanation of these contradictory results may be difficult. However, different subsets of patients with PH are the most likely reason for the different outcome.

The prognosis is poor in SLE patient with PH. Zamora et al. [17] described that factors associated with increased mortality include mechanical ventilation. This may explain the poor prognosis in our study as mechanical ventilation was applied in (7/9) episodes and it was associated with high mortality (6/7) (86%) compared with no deaths in the two episodes in which mechanical ventilation was not employed.

Finally, PH is a rare but lethal complication of SLE and represents a remarkable challenge. It should be diagnosed promptly in the SLE patient with falling red cell indices and new infiltrates on chest radiograph. It occurs in vicinity of active disease and lupus nephritis is the most associated manifestation. Early treatment with IV methylprednisolone and IV cyclophosphamide should be instituted for a better outcome (see Table 12).

Our conclusion is that DAH is a serious manifestation and it should be a part of the differential diagnosis in all SLE patients presenting with hemoptysis and lung infiltrates. In absence of hemoptysis, diffuse pulmonary infiltrates, falling hemoglobin and hemorrhagic BAL confirm the diagnosis. Early recognition and aggressive therapy needs to be started promptly because death from respiratory failure can occur within hours to days of initial presentation.

References

[1] Evans CC. Rheumatic and connective tissue disorders. In: Gibson J, Geddes D, Costabel U, Sterk P, Corrin B, editors. Respiratory medicine. Saunders Ltd.; 2003. p. 2029–42.

[2] Takada H, Saito Y, Nomura A, Ohga S, Kuwano K, Nakashima N, et al Bronchiolitis obliterans organizing pneumonia as an initial manifestation in systemic lupus erythematosus. Pediatr Pulmonol 2005;40(3):257–60.

[3] Orens JB, Martinez FJ, Lynch JP. Pleuropulmonary manifestations of systemic lupus erythematosus. Rheum Dis Clin North Am 1994;20(1):159–93.

[4] Olser W. On the visceral manifestations of the erythema group of skin diseases. Am J Med Sci 2009;338(5):396–408.

[5] Santos Ocampo AS, Mandell BF, Fessler BJ. Alveolar hemorrhage in systemic lupus erythematosus: presentation and management. Chest 2000;118(4):1083–90.

[6] Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25(11):1271–7.

[7] Chang SJ, Yen YS, Huo AP, Lee SS, Huang DF. Acute massive pulmonary hemorrhage after craniotomy in a patient with systemic lupus erythematosus. J Microbiol Immunol Infect 2005; 38(1):69–72.

[8] Chen YC, Chen CY, Tien YC, Fang JT, Huang CC. Organ system failures prediction model in intensive care patients with acute renal failure treated with dialysis. Ren Fail 2001;23(2):207–15.

[9] Bombardier C, Gladman DD, Urowitz MB, Caron D, Chang CH. Derivation of the SLEDAI. A disease activity index for lupus patients. The Committee on prognosis studies in SLE. Arthritis Rheum 1992;35(6):630–40.

[10] Paran D, Fireman E, Elkayam O. Pulmonary disease in systemic lupus erythematosus and the antiphospholipid syndrome. Autoimmun Rev 2004;3(1):70–5.

[11] Pines A, Kaplinsky N, Olchovsky D, Rozenman J, Frankl O. Pleuro-pulmonary manifestations of systemic lupus erythematosus: clinical features of its subgroups. Prognostic and therapeutic implications. Chest 1985;88(1):129–35.
[12] Segal AM, Calabrese LH, Ahmad M, Tubbs RR, White CS. The pulmonary manifestations of systemic lupus erythematosus. Semin Arthritis Rheum 1985;14(3):202–24.
[13] Myers JL, Katzenstein AA. Microangiitis in lupus-induced pulmonary hemorrhage. Am J Clin Pathol 1986;85(5):552–6.
[14] Koh WH, Thumboo J, Boey ML. Pulmonary haemorrhage in oriental patients with systemic lupus erythematosus. Lupus 1997;6(9):713–6.
[15] Liu MF, Lee JH, Weng TH, Lee YY. Clinical experience of 13 cases with severe pulmonary hemorrhage in systemic lupus erythematosus with active nephritis. Scand J Rheumatol 1998;27(4):291–5.
[16] Abud Mendoza C, Diaz Jouanen E, Alarcon Segovia D. Fatal pulmonary hemorrhage in systemic lupus erythematosus. Occurrence without hemoptysis. J Rheumatol 1985;12(3):558–61.
[17] Zamora MR, Warner ML, Tuder R, Schwarz MI. Diffuse alveolar hemorrhage and systemic lupus erythematosus. Clinical presentation, histology, survival and outcome. Medicine (Baltimore) 1997;76(3):192–202.
[18] Haupt HM, Moore GW, Hutchins GM. The lung in systemic lupus erythematosus. Analysis of the pathologic changes in 120 patients. Am J Med 1981;71(5):791–8.
[19] Schwab EP, Schumacher Jr HR, Freundlich B, Callegari PE. Pulmonary alveolar hemorrhage in systemic lupus erythematosus. Semin Arthritis Rheum 1993;23(1):8–15.
[20] Barile LA, Jara LJ, Medina Rodriguez F, Garcia Figueroa JL, Miranda Limon JM. Pulmonary hemorrhage in systemic lupus erythematosus. Lupus 1997;6(5):445–8.
[21] Primack SL, Miller RR, Muller NL. Diffuse pulmonary hemorrhage: clinical, pathologic and imaging features. Am J Roentgenol 1995;164(2):295–300.
[22] Can˜as C, Tobón GJ, Granados M, Fernández L. Diffuse alveolar hemorrhage in Colombian patients with systemic lupus erythematosus. Clin Rheumatol 2007;26(11):1947–9.
[23] Millman RP, Cohen TB, Levinson AI, Kelley MA, Sachs ML. Systemic lupus erythematosus complicated by acute pulmonary hemorrhage: recovery following plasmapheresis and cytotoxic therapy. J Rheumatol 1981;8(6):1021–3.
[24] Albelda SM, Gefter WB, Epstein DM, Miller WT. Diffuse pulmonary hemorrhage: a review and classification. Radiology 1985;154(2):289–97.
[25] Harmon KR, Leatherman JW. Respiratory manifestations of connective tissue disease. Semin Respir Infect 1988;3(3):258–73.
[26] Scwarz MI, Cherniack RM, King TE. Diffuse alveolar hemorrhage and other rare infiltrative disorders. In: Murrary JF, Nadel JA, editors. Textbook of respiratory medicine. W.B. Saunders Company; 1994. p. 1889–912.
[27] Greening AP, Hughes JM. Serial estimations of carbon monoxide diffusing capacity in intrapulmonary haemorrhage. Clin Sci (London) 1981;60(5):507–12.
[28] Hsu BY, Edwards DK, Trambert MA. Pulmonary hemorrhage complicating systemic lupus erythematosus: role of MR imaging in diagnosis. Am J Roentgenol 1992;158(3):519–20.
[29] Makino Y, Ogawa M, Ueda S, Ohto M. CT appearance of diffuse alveolar hemorrhage in a patient with systemic lupus erythematosus. Acta Radiol 1993;34(6):634–5.
[30] Carette S, Macher AM, Nussbaum A, Plotz PH. Severe, acute pulmonary disease in patients with systemic lupus erythematosus: ten years of experience at the National Institutes of Health. Semin Arthritis Rheum 1984;14(1):52–9.
[31] Badsha H, Teh CL, Kong KO, Lian TY, Chng HH. Pulmonary hemorrhage in systemic lupus erythematosus. Semin Arthritis Rheum 2004;33(6):414–21.
[33] Marino CT, Pertschuk LP. Pulmonary hemorrhage in systemic lupus erythematosus. Arch Intern Med 1981;141(2):201–3.
[34] Lee JG, Joo KW, Chung WK, Jung YC, Zheung SH, Yoon HJ, et al. Diffuse alveolar hemorrhage in lupus nephritis. Clin Nephrol 2001;55(4):282–8.
[35] Mintz G, Galindo LF, Fernandez Diez J, Jimenez FJ, Robles Saavedra E, Enriquez Casillas RD. Acute massive pulmonary hemorrhage in systemic lupus erythematosus. J Rheumatol 1978;5(1):39–50.
[36] Leatherman JW. Immune alveolar hemorrhage. Chest 1987;91(6):891–7.
[37] Onomura K, Nakata H, Tanaka Y, Tsuda T. Pulmonary hemorrhage in patients with systemic lupus erythematosus. J Thorac Imaging 1991;6(2):57–61.
[38] Eagen JW, Memoli VA, Roberts JL, Matthew GR, Schwartz MM, Lewis EJ. Pulmonary hemorrhage in systemic lupus erythematosus. Medicine (Baltimore) 1978;57(6):545–60.
[39] Churg A, Franklin W, Chan KL, Kopp E, Carrington CB. Pulmonary hemorrhage and immune-complex deposition in the lung. Complications in a patient with systemic lupus erythematosus. Arch Pathol Lab Med 1980;104(7): 388–91.
[40] Ichikawa Y, Shimizu H, Kobayashi I, Miyairi A, Yamada T, Arimori S, et al Recurrent lupus pneumonitis with pulmonary hemorrhage in systemic lupus erythematosus associated with chronic thyroiditis and antithyroid hormone autoantibodies. Clin Exp Rheumatol 1989;7(3):309–13.
[41] Cooper Jr JA, White DA, Matthay RA. Drug-induced pulmonary disease. Part 1: Cytotoxic drugs. Am Rev Respir Dis 1986;133(2):321–40.
[42] Wu CY, Chiou YH, Chiu PC, Hsieh KS. Severe pulmonary hemorrhage as the initial manifestation in systemic lupus erythematosus with active nephritis. Lupus 2001;10(12):879–82.